REMARKS

Amendments

Specification

The specification has been amended to correct a portion of the statements made therein which are allegedly not consistent with the data disclosed in Table 1. Applicant has deleted the allegedly inconsistent reference. No new matter has been added by this amendment.

Claims

Claims 1-4, 13-16 and 27-29 have been canceled, as they are drawn to non-elected subject matter. Claims 5-12 and 17-26 were canceled in the previous amendment. Claims 30-40 are pending. Claims 30-33, 35-37 and 39-40 have been amended and claims 34 and 38 have been canceled by this amendment.

The amendments to the claims and specification do not add or constitute new matter. Support for the newly added claims may be found throughout the specification and originally filed claims.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are intended to place the claims in condition for allowance in response to the final rejection. The amendments to the claims are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, 30-33, 35-37 and 39-40 are pending in the instant application.

Objections

The Examiner has maintained the objection to the disclosure of the specification because the data disclosed in Example 1, *Embryonic Lethality,* is allegedly unclear. Specifically, the Examiner asserted that the text, which discloses that homozygous mutants are arrested in development and have no somites formed, contradicts the data in Table 1, which the Examiner alleges discloses the presence of somites in one litter. The Applicant again asserts that the row to which the Examiner is referring is a stage where the wild-type embryos have and/or would be expected to have formed 6-9 somites. At this stage, homozygous embryos have been identified,

which embryos are arrested in development, consisting of small, abnormal resporbing egg cylinders resembling embryonic day 7.5. Applicant submits that this is made clear by the statements made in the specification and in Table 1. However, as the Office Action has been made final, Applicant is making a *bona fide* effort to overcome all objections and rejections to the Examiner's satisfaction. Therefore, Applicant has deleted any references to somites in this section of the specification, thus removing any inconsistencies regarding whether somites have formed in the homozygous embryos.

The Applicant submits that, particularly in light of the amendment made to the specification, Example 1 clearly demonstrates the outcome of the disruption of the ubiquitin ligase E3 gene on embryonic development. More particularly, the specification states that the disruption in the ubiquitin ligase E3 gene leads to an embryonic lethality, which Applicant found to occur at or after approximately embryonic day 8.5 (E8.5) – "Homozygous offspring were detected by PCR at E8.5, but not at later stages" (see page 52, line 12). Applicant discloses that homozygous offspring were present at E8.5, as indicated in Litter 2 of Table 1, but that the development of these embryos was arrested, resembling normal embryos at E7.5 (see page 52, lines 13-15), which is what is claimed regarding the transgenic mice. Applicant believes the disclosure contained in Example 1 is clear with regard to the effect of the disruption of ubiquitin ligase E3 on embryonic development in light of what is claimed.

In light of the amendment to the specification, Applicant submits that the data in the disclosure and Table 1 are clear and consistent as the Examiner has required. Therefore, Applicant believes the objection is no longer relevant.

Rejections

Rejection under 35 U.S.C. § 112, first paragraph

1. Written Description

The Examiner has rejected claims 30-40 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Applicant respectfully traverses the rejection.

According to the Examiner, claims 5-12 and 17-26 encompass more than one ubiquitin ligase E3 gene, and more particularly, encompass any mouse ubiquitin ligase E3 gene. The

Examiner has alleged that the specification has only described the mouse ubiquitin ligase E3 gene set forth in SEQ ID NO:1. The Examiner has stated in the Office Action that disruption of a ubiquitin ligase E3 gene distinct from that set forth in SEQ ID NO:1 results in a "vastly different phenotype with no obvious correlation to the phenotype effected by disruption of SEQ ID NO:1." See page 4 of the Office Action.

The Examiner has suggested that amending the claims to read on the nucleotide sequence set forth in SEQ ID NO:1 may be sufficient to overcome this rejection. Applicant has adopted the Examiner's suggested modification in order to overcome the rejection. As amended, the claims now read on a disruption of the ubiquitin ligase E3 gene set forth in SEQ ID NO:1. Therefore, the rejection of claims 30-40 is no longer relevant, and Applicant respectfully requests withdrawal of the rejection.

Applicant submits that the pending claims are patentable and meet the written description requirements set forth in the first paragraph of 35 U.S.C. § 112.

2) Enablement

The Examiner has rejected claims 30-40 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses this rejection.

Specifically, the Examiner claims that the specification while being enabling for a transgenic mouse embryo whose genome comprises a homozygous disruption in the endogenous mouse ubiquitin ligase E3 gene set forth in SEQ ID NO:1 wherein said embryo exhibits embryonic lethality, does not reasonably provide enablement for a transgenic mouse or mouse embryo whose genome comprises a disruption in any endogenous mouse ubiquitin ligase E3 gene wherein the disruption is heterozygous.

Regarding claims 31-37, the Examiner asserts that these claims encompass postnatal mice. Applicant argues that these claims should incorporate the limitations set forth in the parent claim 30. However, in order to overcome this issue, Applicant has amended the claims to recite the term embryo. Therefore, the Applicant has overcome this aspect of the rejection.

The Examiner alleges that claims 30-40 encompass a transgenic mouse comprising a heterozygous disruption and cells or tissues derived from said mouse. Although Applicant disagrees with the Examiner's conclusion, these claims have been amended to more particularly

recite the homozygous disruption in the transgenic mouse embryo, which is enabled by the specification according to the Examiner.

The Examiner has alleged that claims 30-40 broadly encompass multiple endogenous ubiquitin ligase E3 genes, while the specification teaches disruption only of the gene set forth in SEQ ID NO:1. Applicants disagree, and maintain the assertion that the specification clearly sets forth which gene has been disrupted. However, the claims have been amended to recite that the ubiquitin ligase E3 gene set forth in SEQ ID NO:1 was disrupted in the claimed mice. Therefore, this issue of enablement is no longer relevant.

As noted above, the amendments to or cancellation of claims overcome each issue of enablement raised by the Examiner in the rejection. Therefore, the Examiner's rejection under 35 U.S.C. § 112, first paragraph is no longer relevant. Applicant respectfully requests withdrawal of the rejection.

Applicant submits that the pending claims fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 31-37 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant respectfully traverses this rejection.

Specifically, the Examiner asserts that the claims refer to "The transgenic mouse" of claim 30, for which term there is insufficient antecedent basis. As noted above, the pending claims now recite a transgenic mouse "embryo." Therefore, the rejection has been overcome.

Applicant submits that the pending claims are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 5, 6, 8 and 9 under 35 U.S.C. § 102(b) as being anticipated by Perry, 1998, *Nature Genetics,* 18: 143-146 ("Perry") as it relates to newly added claims 30-40, and in particular to claims 30-38. Applicant respectfully traverses this rejection. However, Applicant submits that the amendments to the claims overcome the rejection.

Perry, according to the Examiner, teaches a mouse comprising a disruption in the *Itch* locus, which encodes a ubiquitin ligase E3 gene. The Examiner alleges that the mice disclosed in

Perry meet the instant claim limitations of a genome comprising a homozygous disruption of the endogenous mouse ubiquitin ligase E3 gene, despite that the Perry mice exhibit phenotypes that differ from the claimed mouse.

Claims 30-33, 35-37 and 39-40, as amended, are drawn to a transgenic mouse embryo comprising a disruption in the endogenous mouse ubiquitin ligase E3 gene set forth in SEQ ID NO:1, wherein the transgenic mouse exhibits an increased incidence of lethality during embryonic development, methods of producing the mouse, and cells and tissues derived from the mouse. Perry clearly fails to teach every claim limitation recited in these pending claims. In particular, Perry fails to meet the instant claim limitations. More particularly, Perry relates to disruption of the *Itch* locus which encodes a ubiquitin ligase E3, whereas the claimed invention relates to the ubiquitin ligase E3 set forth in SEQ ID NO:1. Perry fails to teach or suggest the specific gene as set forth in SEQ ID NO:1 and recited in the pending claims, and in fact teaches an entirely different gene. Further, Perry does not teach that disruption of the ubiquitin ligase E3 gene set forth in SEQ ID NO:1 results in the lethal phenotype of the transgenic mouse as recited in the pending claims.

As the rejection under 35 U.S.C. § 102(b) is no longer relevant as a result of the amendments to the claims, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102. Applicant submits that the claims, as amended, are not anticipated by the teachings of Perry.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-441.

Respectfully submitted,

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